CHAPTER 7

Summary and Future Outlook

This PhD work began with the aim to explore any role of electron-correlation (the instantaneous interactions between the electrons) in the origin of biological response of chemicals, which was achieved by developing the quantum-chemical descriptors based externally predictive QSAR models for biological activities of the chemicals. In the present work, mainly the hazardous biological activities, like the mutagenicity and toxicity of various chemicals were modeled. The significance of the proposed QSAR models is assured through the rigorous statistical validation procedures employing the state-of-the-art external validation parameters using an external prediction set of chemicals. This thesis proposes that the incorporation of the effect of electron-correlation in the quantum-chemical descriptors can be a reliable variable for the QSAR models and can have considerable future applications in modeling biological activities of the chemicals.

This thesis successfully demonstrated the first-ever use of the electron-correlation energy and its contribution to the HOMO energy for developing the externally predictive QSAR models for the frame-shift mutation observed in the TA98 strain of *S. typhimurium* by the hazardous chemicals like nitrated – PAHs. In fact, this study, presented in chapter 2 of the thesis, observed that the models based on the quantum-chemical descriptors incorporating the electron-correlation are more robust than the models developed with the whole descriptors computed using the HF and DFT methods. Furthermore, in this study, the models based on the descriptors computed with the advanced semi-empirical methods, namely the RM1 and PM6 are also found to be reliable.

The chapter 3 of the thesis, further extended the investigation, on the electron-correlation to look at if it is also significant while modeling another type of mutagenicity, since a chemical inactive in one strain cannot be expected as non-mutagenic because it can be active in other strains also. For this, the base-pair mutagenicity of the nitrated – PAHs shown in TA100 strain of *S. typhimurium*, is modeled with the descriptors based on the electron-correlation. For this work, besides the correlation energy, the electron-density based quantum-chemical descriptors were also employed which includes the chemical hardness, chemical softness, absolute electronegativity, and electrophilicity index along with their respective electron-correlation contribution. In this study also, the models based on the
descriptors incorporating the effects of electron-correlation are found to be more reliable than those developed with the HF and DFT computed descriptors. Though the robustness of the models based on the descriptors computed through the advanced semi-empirical methods, is also observed to be comparable to those developed with the electron-correlation based descriptors. In this study, the electron-correlation contribution from the electrophilicity along with the total energy and energy of the HOMO are observed as the most reliable descriptors for modeling the mutagenicity.

Besides investigating the role of electron-correlation towards the external predictivity of the QSAR models, the thesis also explored the role of quantum-mechanical exchange interactions in QSARs as presented in chapter 4 of the thesis. For this, the performance of various exchange-correlation functionals of the DFT is analyzed towards the computation of reliable descriptors for the QSAR. For this study also, the mutagenicity of nitratad PAHs in both TA100 and TA98 strains of S. typhimurium is chosen as the modeled response. A comparison of the quality of the models developed with the descriptors computed using the DFT employing different XC functional and electron-correlation based descriptors revealed that the exchange interactions can be quite critical along with the electron-correlation in modeling the mutagenicity, however, the incorporation of the electron-correlation is quite significant in the QSAR models in order to have low errors in the external prediction.

Further, in chapter 5, to test our hypothesis on the role of electron-correlation, the thesis attempted to develop the QSAR models for the acute toxicity of 252 diverse chemicals against the Daphnia magna which is one of the most challenging task for the QSAR modelers. In this work, besides the descriptors based on the electron-correlation, a few physico-chemical, topological and electrostatic descriptors were also employed. A comparison of the robust models based on the various quantum-chemical descriptors suggests that the electron-correlation based descriptors can have a role in the modeling of the acute toxicity though the advanced semi-empirical computed descriptors were found to be more reliable which are also computationally less expensive. For modeling the acute toxicity of diverse chemicals, total energy and energy of HOMO along with physico-chemical and topological descriptors were observed to be quite significant.

Finally, after establishing the role of electron-correlation in the quantitative modeling of mutagenicity and acute toxicity as presented in chapters 2-5 of the thesis, chapter 6 of the thesis, further extended the application of electron-correlation to the modeling of toxicity of alkyl- and halogen-substituted nitro- and dinitrobenzenes towards the Tetrahymena.
Here again, augmenting our investigation in previous chapters, the models incorporating the effect of electron-correlation contribution from the descriptors are found to be significantly robust and predictive, in particular, the models incorporating the electron-correlation contribution from the total energy and electron density based descriptors.

Overall, this thesis, through the QSARs, was able to reveal an unexplored phenomenon involving the effect of electron-electron interactions towards the biological response. However, while performing the research work, it was observed that the quantum-chemical descriptors, particularly computed using the advanced quantum-mechanical theories, are not very much explored in the literature for modeling the activity of a drug like chemicals. This might be due to the reason that the drug molecules have complex and relatively large molecular structure which effectively increases the computational cost in terms of time and resources. As observed in this thesis, if the quantum-mechanical quantities, such as electron-correlation is incorporated for modeling the activities of drug like chemicals then new better correlation between the structure of drugs and their activities can be expected. Therefore, in the future, the work performed in this thesis can be applied to model the activities of drug like chemicals, and to investigate if the electron-correlation can be significant in modeling the properties of drugs as it is observed while modeling the mutagenicity and toxicity of the chemicals. Further, during such studies, interaction of chemical with the different biological enzymes and proteins can also be studied. Furthermore, this thesis mainly focused on the hazardous biological activities of the chemicals, in the future work, attempt can be made to model activities such as absorption through cell lines, binding affinities with biomolecules, using the quantum-chemical descriptors incorporating the effect of electron-electron interactions. The work presented in this thesis has vast potential in the field of pharmaceutical and environmental sciences with tremendous applications waiting to be explored.